**Kaur H, Dutta P, et al. A Comparative Evaluation of Amitriptyline and Duloxetine in Painful Diabetic Neuropathy. Diabetes Care 2011;34:818-822.**

Design: Randomized crossover trial

Population/sample size/setting:

- 58 Type 2 diabetics (27 men, 31 women, mean age 52) completed a clinical trial for painful diabetic neuropathy (PDN) in a department of pharmacology in India
- Inclusion criteria were PDN lasting at least one month, with a VAS pain score ">50%," with stable glucose control for at least one month
    - PDN determined by history, examination, and increased vibration perception threshold on a monofilament test
- Exclusion criteria were other causes of neuropathy, renal insufficiency, other unstable medical or psychiatric illness, substance abuse, epilepsy, pregnancy, and taking other investigational drugs within the previous 30 days
- Patients taking other medications for PDN were eligible for the study after a 2-week washout period

Main outcome measures:

- A crossover trial was done comparing amitriptyline and duloxetine, with a 2 week placebo run-in followed by 6 weeks on one drug, a 2 week washout, and 6 weeks on the other drug; this was followed by a 4-week placebo single-blind run-out phase
- Primary outcome was reduction in pain scores on a 100 point VAS
- Amitriptyline was administered as either 10, 25, or 50 mg doses; duloxetine was administered at either 20, 40, or 60 mg doses; all drugs were taken at bedtime, and titration of doses took place every 2 weeks, depending on tolerability and response
- Median pain score reductions were classified as good, moderate, and mild; "good" meant reduction >50%, "moderate" meant 25-50%, and "mild" meant <25% reduction in VAS
- Good, moderate, and mild reductions were similar in the two groups: for duloxetine, the percentages were 59%, 22%, and 9%; for amitriptyline, the percentages were 55%, 24%, and 16%
- Overall pain relief >30% for duloxetine was 64% of patients, and was 62% for amitriptyline
- Adverse effects were more common with amitriptyline than with duloxetine; dry mouth was the main side effect that was more common with amitriptyline
- Glycemic control and weight were stable during the course of the trial
- During the 4-week run-out at the end of the study, pain VAS increased from a median of 26 to a median of 40 over an average period of observation of 21 days
- Secondary analyses (sleep quality) showed similarity between the 2 drugs
- A few more patients expressed a preference for duloxetine than for amitriptyline, but this difference was not statistically significant

Authors' conclusions:

- Amitriptyline and duloxetine demonstrated comparable efficacy, safety, and tolerability for management of PDN
- A larger head-to-head trial could possibly demonstrate the superiority of one or the other drug

Comments:

- Several things are unclearly or inadequately described, creating some difficulties in interpretation of the study
- The exclusion criteria include "taking anticonvulsants, antidepressants, local anesthetics, or opioids;" however, the inclusion criteria indicate that these patients were eligible after a 2-week washout period
- Success of blinding was apparently assessed by the accuracy of a physician's prediction at the end of the study (during the run-out?), but this is not clearly described, since it would require a retrospective evaluation of drug effects during both of the treatment periods, as well as during the placebo run-out phase of the study
- The medications were supplied by the manufacturer as free samples, which would create problems with blinding
    - Presumably, the appearance of the drugs is different, assuming that there are manufacturing standards which require that oral medications be identifiable by appearance
- There is an assertion in the text that the baseline scores were similar in the two groups "before and after the crossover," meaning at the beginning of both treatment periods
    - Figure 2 shows the scores graphically, but the accompanying table shows the number of participants at each week of the study, rather than the VAS scores; this duplicates the information in Figure 1, but adds no information about the actual scores
    - At week 10 (the beginning of the second treatment period), the scores for the amitriptyline-first group and the duloxetine-first group would appear to be identical; the lack of reported numerical scores makes this difficult to interpret
    - Figure 2 shows what might be a period effect (duloxetine better than amitriptyline in the first period; the two drug effects much more similar in the second period); there should be a discussion of this issue, since the figure may be misleading
- There is not sufficient information to make for evidence of equivalence between the two drugs, but a clear superiority of duloxetine is also not supported by the data

Assessment: for evidence that duloxetine has not been shown to be superior to amitriptyline for neuropathic pain treatment: adequate
For evidence that amitriptyline has been shown to be equivalent to duloxetine for neuropathic pain treatment: inadequate